9. The method of any one of claims 1-4 wherein the agent is membrane permeable.

REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 1-40 are pending and Group I, claims 1-11 and 22-40 directed to a method for treating diabetes, was elected for prosecution in the Response to Restriction Requirement filed on March 28, 2002, with the further election of the species identified as "Cpd. No. 1". Accordingly, claims 12-26 and 35-40 have been withdrawn from consideration, and claims 1-11 and 27-34 are currently under examination. Claim 1 has been amended to more particularly point out and distinctly claim subject matter which applicants regard as encompassed by the invention. Support for this amendment may be found in the specification, for example, at page 23, lines 3-13; page 37, line 23 through page 38, line 3; page 52, lines 5-13; page 53, line 17 through page 54, line 12; and page 56, line 6 through page 57, line 27. Claim 9 has been amended, without limitation, solely for purposes of correcting a deficiency in antecedent basis. No new matter has been added. Attached hereto is a marked-up version of the changes made to the claims by the current Amendment, the first page of which is captioned "Version with Markings to Show Changes Made."

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-11 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. More specifically, the Action asserts that the specification is not commensurate with the scope of the claims, where only Compound Number 1 is enabled, but not other mitochondrial Na+/Ca2+ exchanger antiporters (*sic*). The Action asserts further that undue experimentation would be required to practice the claimed invention, alleging in particular that the specification does not establish criteria for what are "mitochondrial Na+/Ca2+ exchanger antiporters" and that only a limited number of "mitochondrial Na+/Ca2+ exchanger antiporters"

examples are set forth without a definition for this class of compounds, such that an exhaustive search would be required to identify embodiments suitable for practicing the invention.

Applicants respectfully traverse these grounds for rejection. The present invention is directed in pertinent part to a method for treating diabetes mellitus, comprising administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity, in an insulin secreting cell (claim 1) or wherein the agent enhances insulin secretion (claims 2-4), and to related methods.

Applicants are somewhat puzzled by repeated reference at pages 3-4 of the Action to "mitochondrial Na+/Ca2+ exchanger antiporters", where the Action appears to confuse "antiporters" with "compounds", such as Cpd. No. 1. Cpd. No. 1 is an example of an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity, but Cpd. No. 1 is not itself a "mitochondrial Na+/Ca2+ exchanger antiporter." Cpd. No. 1 was previously elected by Applicants as the species for initial examination in the response, filed on March 28, 2002, to a requirement for election of species that accompanied the Restriction Requirement in the Office Action mailed by the PTO on March 8, 2002. Accordingly, and contrary to the assertion in the Action, a large number of agents that selectively impair a mitochondrial calcium/sodium antiporter activity, and not just Cpd. No. 1, are clearly enabled by the instant specification (*e.g.*, page 11, line 17 through page 21, line 28; pages 42-51; page 56, lines 27-28; page 57, lines 20-27).

Moreover, the specification clearly describes well known mitochondrial Na^+/Ca^+ transport *activities* by which calcium cations are stoichiometrically exchanged for sodium cations across the mitochondrial membrane (*e.g.*, page 2, line 27 through page 3, line 4, including references cited therein; page 6, lines 2-20, including references cited therein). The specification also teaches how specifically to determine mitochondrial calcium/sodium antiporter (MCA) *activity*, and how to distinguish such activity from other transport activity, where such MCA *activity* is well described. Thus, methodologies in which extramitochondrial sodium cations are capable of stimulating detectable mitochondrial Ca^{2+} efflux are described abundantly and in enabling fashion for the person skilled in the art (*e.g.*, specification at page 2, line 27 through

page 3, line 4; page 26, line 21 through page 28, line 2; page 34, line 28 through page 35, line 9; page 35, line 22 through page 36, line 7; page 36, lines 22-24; page 52, line 15 through page 53, line 16; page 56, lines 6-28), including determination that MCA activity is *selectively* impaired (*e.g.*, that Ca^{2+} efflux is Na^{+}-driven). Applicants therefore submit that whether an agent "selectively impairs a mitochondrial calcium/sodium antiporter *activity*" (emphasis added) can be defined on the basis of such "activity", as provided by the instant specification.

Applicants therefore also traverse the allegation in the Action that the specification does not establish criteria for what are "mitochondrial Na^{+}/Ca^{2+} exchanger antiporters", where the invention relates in pertinent part to mitochondrial calcium/sodium antiporter *activity*. For reasons discussed above, the instant application more than amply provides criteria for determining when, as disclosed in the specification and as recited in the claims, "an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity" is present. Moreover, the specification provides ample teachings of agents that selectively impair a mitochondrial calcium/sodium antiporter activity (*e.g.*, specification at page 11, line 17 through page 20, line 17; page 33, lines 25-28; page 35, line 10 through page 38, line 10; pages 42-51; page 56, lines 27-28; page 57, lines 20-27).

Applicants disagree with the assertion in the Action (at page 4) that "each embodiment [must] be individually assessed for physiological activity" where "[t]he instant claims read on all 'mitochondrial Na+/Ca+ exchanger antiporter(s)'". As discussed above, the present invention relates to mitochondrial calcium/sodium antiporter *activity*. Additionally, the Federal Circuit noted in *In re Brana* that usefulness in the context of pharmaceutical inventions and the requirements of 35 U.S.C. § 112 includes the expectation of further research and development. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). The Board of Patent Appeals and Interferences also determined that *in vitro* studies may be adequate to overcome rejections under 35 U.S.C. § 112. *Ex parte Chwang*, 231 USPQ 751 (BPAI 1986).

In the instant application, *in vitro* results are presented demonstrating that applicants have possession of the invention that is disclosed in the specification and recited by the instant claims. For example, Examples 6 (pages 52-53) and 9 (page 56) teach identification of agents that selectively impair a mitochondrial calcium/sodium anitporter activity, and Examples 7 (pages 53-54) and 10 (page 57) describe the effects of such agents on insulin

secretion by primary cultures of pancreatic islet cells, which effects are beneficial and desirable in the context of treating diabetes mellitus. Applicants submit that such agents would reasonably be recognized by a person skilled in the art as useful in the claimed method of treating diabetes mellitus, given the relationship between impairment of mitochondrial MCA activity and insulin secretion that is established for the first time according to the present invention. Moreover, *In re Brana* holds that the PTO bears the burden of challenging a presumptively correct assertion of utility in a patent application by providing evidence showing that a person skilled in the art would reasonably doubt the asserted utility. Therefore, applicants respectfully submit that the methods and experimental data disclosed in the instant specification, in view of the state of the relevant art, convey to one having skill in the art that the inventors had possession of the claimed invention at the time the application was filed.

Accordingly, applicants respectfully submit that the instant specification provides sufficient guidance to enable a person having ordinary skill in the art to make and use the claimed invention, that the disclosure of the subject specification is commensurate with the scope of the claims and that no undue experimentation is required to practice the invention. Applicants submit further that the level of skill in the relevant art is high, with practitioners typically holding a Ph.D. or the equivalent, and that working examples are in fact provided, as described above. Furthermore, the state of the art is such that at the time of filing the instant application, a person skilled in the art would have been able readily to determine whether an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity is present, given the teachings of the present specification and the state of the art at the time of filing. Enablement is not precluded by the necessity for some experimentation, such as routine screening (*In re Wands*, 8 U.S.P.Q.2d 1404, Fed. Cir. 1988).

Applicants therefore respectfully submit that the present application satisfies all requirements of 35 U.S.C. §112, first paragraph, and request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-11 stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. More specifically, the Examiner is unclear regarding the meanings of the recitations "suspected of being at risk for having diabetes", "agent that selectively impairs a

mitochondrial calcium/ sodium antiport (*sic*) activity" and "maturity onset diabetes of the young". The Action also asserts insufficient antecedent basis for the limitation "the candidate agent" in claim 9.

Applicants respectfully traverse these grounds for rejection. With regard to "suspected of being at risk for having diabetes" and "maturity onset diabetes of the young" (MODY), applicants submit that the meanings of these recitations are clear as provided by the specification, for example, at page 1, line 23 through page 2, line 10, wherein are described a variety of phenotypes that may be characteristic of a risk for predisposition to diabetes mellitus, including indicators of altered mitochondrial respiratory function, impaired glucose tolerance, decreased release of and sensitivity to insulin, obesity, vascular pathologies and neuropathies.

The specification also teaches a variety of well known criteria that have been established for determining a risk for having diabetes mellitus, or for identifying MODY, which will be readily understood to the skilled practitioner interested in identifying a risk for diabetes in a subject, for example, at page 22, line 25 through page 25, line 8, including references cited therein. Accordingly, levels of circulating insulin, proinsulin, glucose or other biomarkers known to the art may be detected under defined conditions (*e.g.*, fasting, basal metabolic, non-fasting, glucose-stimulated, active, dietary or other conditions), in order to identify a risk for having diabetes, and/or to determine MODY, according to accepted clinical signs and symptoms for these conditions. As these and other art-accepted criteria will be familiar to those skilled in the diabetes art, applicants submit there can be no ambiguity concerning whether a subject will be suspected of being at risk for having diabetes.

Turning to the recitation "agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity", applicants respectfully submit that given the present specification, the meaning according to the instant claims is also unambiguous. Agents according to the invention are clearly described in the specification, for example, at page 35, line 10 through page 38, line 10. Furthermore, an agent that selectively impairs MCA function is described, for example, at page 36, line 22 through page 37, line 3, wherein such agent is described as selectively decreasing mitochondrial MCA function in a statistically significant manner, without significantly affecting other normal cellular physiologic calcium transporters, such as plasma membrane calcium channels or other extramitochondrial calcium transport molecules, or the

mitochondrial calcium uniporter. As also described above, MCA activity can be distinguished from that of such other calcium transporters according to the teachings of the present application, including, *inter alia*, the ability to induce mitochondrial Ca^{2+} efflux by exposure of mitochondria to Na^{+}. Applicants therefore submit that from the descriptions in the instant specification and for reasons already discussed above, the skilled artisan readily understands whether or not a candidate agent is an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity.

Applicants thank the Examiner for calling to applicants' attention the issue concerning antecedent basis in claim 9, and respectfully submit that the rejection is obviated by the amendment to claim 9 as submitted herewith.

Accordingly, applicants submit that the present application satisfies all requirements of 35 U.S.C. §112, second paragraph, and request that these rejections be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-11 and 27-34 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Kennedy et al. (1996 *J. Clin. Invest.* 98:2524) and Cox et al. (1993 *Trends Pharmacol. Sci.* 21:595). In the Action, the PTO asserts that Kennedy et al. teach dependency of insulin secretion on cellular glucose levels and related elevation of cytosolic and intramitochondrial Ca^{2+} levels, such that a skilled artisan would recognize increased insulin levels in response to elevated glucose as a treatment for diabetes. The PTO asserts further that Cox et al. teach that the elected compound, CGP-37157, is a mitochondrial Na^{+}/Ca^{2+} exchanger antagonist that would be expected to increase intramitochondrial Ca^{2+} concentration. The Action concedes that the references fail expressly to teach CGP-37157 as an oral diabetes therapy. The PTO alleges, however, that a person having ordinary skill in the art would have been motivated to administer CGP-37157 to treat diabetes, based on an expectation from the teachings of Kennedy et al. that increasing the intramitochondrial Ca^{2+} level in response to elevated glucose would provide increased insulin.

Applicants respectfully traverse these grounds for rejection. As noted above, the present invention is directed in pertinent part to a method for treating diabetes mellitus,

comprising administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity, in an insulin secreting cell (claim 1) or wherein the agent enhances insulin secretion (claims 2-4), and to related methods.

Applicants respectfully submit that the PTO has failed to establish a case of *prima facie* obviousness, where for reasons discussed in greater detail below, the references cited by the Action, alone or in combination, fail to teach or suggest the subject matter of the instant claims. (*See In re Mayne*, 104 F.3d 133, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (PTO has the burden of showing a *prima facie* case of obviousness.)). The PTO must show (1) that the combined references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, a teaching, motivation, or suggestion to combine the references must exist. (*See In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

Furthermore, applicants respectfully submit that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g.*, *In re Mills*, 16 USPQ2d 1430, Fed. Cir., 1990; *In re Fritch*, 23 USPQ2d 1780, Fed. Cir., 1992). Thus, applicants respectfully submit that the PTO has not set forth a *prima facie* case of obviousness, where the references cited in the Action fail to teach every limitation of the instant invention and where the cited references also fail to provide motivation for a person having ordinary skill in the art to modify or combine the teachings found therein to arrive at the claimed invention with a reasonable expectation of success.

The teachings of Kennedy et al. relate to mitochondrial and cytosolic Ca^{2+} levels in a diabetes-relevant cell, the INS-1 pancreatic beta cell line, but Kennedy et al. fail in any way

to suggest selective impairment of a mitochondrial calcium/sodium antiporter activity in a method for treating diabetes, as is the focus of claims 1-4 and claims dependent therefrom. Applicants submit that Kennedy et al. are silent with regard to the nature of any particular *mitochondrial* calcium transport activity and, in fact, do not mention the mitochondrial calcium/sodium antiporter anywhere in their publication. Instead, Kennedy et al. suggest that the changes in mitochondrial calcium levels reported by them may be a result of calcium transport through *plasma membrane* channels (see, *e.g.*, page 2530, 2nd column, 4th paragraph, lines 1-5; page 2535, 1st and 2nd paragraphs). Accordingly, Kennedy et al. fail specifically to contemplate selective impairment of mitochondrial calcium/sodium antiporter activity as useful for treating diabetes, relative to any other mitochondrial calcium transporter activity.

This deficiency in Kennedy et al. cannot be cured by Cox et al. to arrive at the presently claimed invention, in part because Kennedy et al. fail to provide any motivation to combine the teachings found therein with those of Cox et al. In particular, where Kennedy et al. address only an inhibitor of a *plasma membrane* calcium transporter, SR7037, the failure of Kennedy et al. to contemplate blocking any *mitochondrial* calcium transporter, such as a mitochondrial calcium/sodium antiporter, would not have motivated one of ordinary skill to seek a teaching *specifically* related to mitochondrial calcium/sodium antiporter activity. In addition, Kennedy et al. at page 2533, 2nd column, lines 6-15, teach that mechanisms regulating calcium transport and subcellular distribution are different in insulin secreting cells as compared to other cell types, which further supports the lack of motivation that would be felt by one of ordinary skill to combine the Kennedy et al. reference directed to insulin-secreting cells with the Cox et al. reference directed to myocytes, to reach the presently claimed invention. Therefore, applicants submit an ordinarily skilled artisan would have lacked any motivation to combine Kennedy et al. with Cox et al., and so could not reasonably have expected to reach the presently claimed invention.

Cox et al. merely describe regulation of mitochondrial and cytosolic Ca^{2+} levels via the mitochondrial calcium/sodium exchanger in cardiac myocytes, a cell type which is not an insulin secreting cell. Hence, Cox et al. are silent with regard to the use of an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity in an insulin-secreting cell, as recited in claim 1 and claims dependent therefrom. Additionally, Cox et al. are silent

with regard to the use of an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity wherein the agent enhances insulin secretion, as recited in claims 2-4 and claims dependent therefrom. Furthermore, nowhere in the disclosure of Cox et al., alone or in combination with Kennedy et al., can there be found any suggestion to impair a mitochondrial calcium/sodium antiporter activity in an insulin secreting cell, or to impair a mitochondrial calcium/sodium antiporter activity with an agent that enhances insulin secretion, in a method for treating diabetes. Neither can there be found any suggestion whatsoever in Cox et al. that the teachings of Cox et al. might be desirably combined with Kennedy et al., or with any other reference, to provide a method for treating diabetes mellitus according to the present invention.

The teachings of Cox et al. therefore relate at most to mitochondrial calcium/sodium antiporter activity as it pertains to myocardial function. Cox et al., however, fail to teach or suggest any relationship between cardiac myocyte mitochondrial calcium/sodium antiporter activity and circulating and cellular levels of the established diabetes-related metrics insulin and/or glucose. Therefore, Cox et al., alone or in combination with Kennedy et al., cannot be regarded as providing the requisite motivation to arrive at the presently claimed method for treating diabetes mellitus with a reasonable expectation of success.

Applicants respectfully submit that a person having ordinary skill in the art at the time of filing the instant application would have had no motivation to combine the Kennedy et al. and Cox et al. references, for reasons discussed herein. Even assuming, *arguendo*, that the two cited references were combined, applicants submit that the person having ordinary skill in the art would have no reasonable basis for expecting successfully to arrive at the presently claimed invention by such combination. Such ordinarily skilled artisan could not reasonably expect to succeed in treating diabetes by administering an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity in an insulin-secreting cell, or wherein the agent enhances insulin secretion, because given the state of the art, it could not be predicted whether mitochondria in treated cells would compensate for impairment of a mitochondrial calcium/sodium antiporter activity by exporting Ca^{2+} via an alternative transport mechanism. In particular, without the teachings of the instant application, a person having ordinary skill in the art could not know, with a reasonable expectation of success, which of multiple possible mitochondrial calcium transport channel activities would be present in cells or tissues that are

relevant to diabetes, such as insulin secreting cells. Applicants therefore submit that the PTO employs impermissible hindsight in its allegation that the claimed invention would be obvious over Kennedy et al. and Cox et al.

As known in the art and described in the present application, mitochondria possess multiple activities for transporting calcium cations across the inner mitochondrial membrane, including (i) mitochondrial calcium/sodium antiporter (MCA) activity and also including (ii) a sodium-independent calcium transport activity and (iii) the mitochondrial calcium uniporter (*e.g.*, specification at page 2, line 22 through page 3, line 4 ; at page 5, line 26 through page 6, line 20; *see also*, *e.g.*, Fiskum and Lehninger, 1979 *J. Biol. Chem.* 254:6236; Gunter et al., 1994 *Am. J. Physiol.* 267(2pt1):C313-339). As also known to the art, MCA activity varies widely among different cell types and tissues, and is in fact absent from certain tissues. (Crompton et al., 1978 *Eur. J. Biochem.* 82:25; Bernardi, 1999 *Physiol. Rev.* 79:1127; Griffiths et al., 1997 *Cell Calcium* 21:321) For instance, MCA activity is not detectable in kidney, lung or smooth muscle cells, and is quite low in liver. Hence, it would follow that certain cells or tissues that do not possess mitochondrial calcium/sodium antiporter activity could not reasonably be expected to exhibit elevated intramitochondrial Ca^{2+} levels in response to an agent that selectively impairs mitochondrial calcium/sodium antiporter activity. Applicants therefore submit that absent the present application, there would have been no basis for expecting successfully to treat diabetes mellitus by impairing a mitochondrial calcium/sodium antiporter activity in an insulin secreting cell, given the references cited in the Action.

Thus, the art cited by the PTO fails to teach or suggest that mitochondrial calcium/sodium antiporter activity is present in insulin secreting cells or tissues that are relevant to diabetes. Also, contrary to the assertion made by the PTO, a person having ordinary skill in the art would not, at the time the instant application was filed, reasonably have expected to elevate intramitochondrial Ca^{2+} in an insulin secreting cell by administering an agent that selectively impairs a mitochondrial calcium/sodium antiporter activity, given that the art had established that mitochondria possess multiple independent transport mechanisms by which Ca^{2+} can be exported from mitochondria.

Applicants therefore respectfully submit that the Action has not set forth a *prima facie* case of obviousness. As discussed above, the cited references fail to provide a suggestion

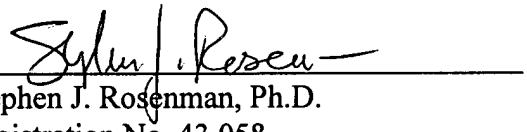
or motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success. Accordingly, applicants respectfully request that this rejection be withdrawn.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner does not believe the claims are allowable for any reason, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

Christen M. Anderson et al.

SEED Intellectual Property Law Group PLLC



Stephen J. Rosenman, Ph.D.
Registration No. 43,058

SJR:kw

Enclosures:

- Postcard
- Check
- Transmittal Form PTO/SB/21
- Fee Transmittal Form PTO/SB/17 (+ copy)
- Petition for Extension of Time
- Second Supplemental IDS
- Form PTO-1449 and Cited References (5)

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

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Version with Markings to Show Changes Made

Claims 1 and 9 are amended as follows:

1. (Amended) A method for treating diabetes mellitus, comprising:

administering, to a subject having or suspected of being at risk for having diabetes mellitus, a therapeutically effective amount of a pharmaceutical composition comprising an agent that selectively impairs a mitochondrial calcium/ sodium antiporter activity in an insulin secreting cell.

9. (Amended) The method of any one of claims 1-4 wherein the ~~candidate~~ agent is membrane permeable.

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